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5 January 2004

***VIA EXPRESS MAIL, WITH RETURN POSTCARD ENCLOSED***

PCT International Application Processing Div.  
USPTO International Division  
Assistant Commissioner for Patents  
Mail Stop PCT  
PO Box 1450  
Alexandria, VA 22313-1450

Re: International Application No. PCT/US03/17825  
Title: METHODS OF DIAGNOSING AND TREATING DIABETES AND INSULIN RESISTANCE  
Applicant: METABOLEX, INC.  
International Filing Date: 04 June 2003  
Express Mail Label No.: EV 332 022 204 US  
Date of Mailing: 05 January 2004  
Our File No.: 16325-140PC

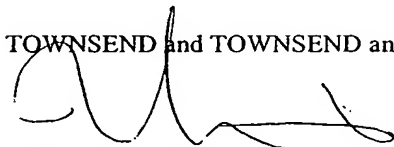
Dear Officer:

Enclosed is the Chapter II Demand for the above-referenced application. Also enclosed are twelve (12) substitute pages 25, 45, 109, 110, 111, 112, 128, 129, 130, 131, 132 and 133 of the specification submitted as an Article 34 Amendment. The changes to the pages are insertions of SEQ ID: NOs and correction of typographical errors. These changes do not go beyond the disclosure of the application as filed.

Thank you for your attention to this matter.

Respectfully submitted,

TOWNSEND and TOWNSEND and CREW LLP



Matthew E. Hinsch  
Reg. No. 47,651

Enclosures: Chapter II Demand  
Twelve (12) Sub. Specification pages (25, 45, 109, 110, 111, 112, 128, 129, 130, 131, 132, 133)  
One hundred and sixty-two (162) pages of Sequence Listing  
Diskette and Statement  
Transmittal Letter  
Postcard

60111100 v1

The demand must be filed directly with the competent International Preliminary Examining Authority if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

# PCT

## CHAPTER II

### DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>		Applicant's or agent's file reference	
		16325-140PC	
International application No.	International filing date (day/month/year)	(Earliest) Priority date (day/month/year)	
PCT/US03/17825	04 June 2003 (04.06.03)	04 June 2002 (04.06.02)	
Title of invention			
METHODS OF DIAGNOSING AND TREATING DIABETES AND INSULIN RESISTANCE			
<b>Box No. II APPLICANT(S)</b>			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)		Telephone No.:	
METABOLEX, INC. 3876 Bay Center Place Hayward, CA 94545 United States of America		510.293.8800	
		Facsimile No.:	
		510.293.9090	
		Teleprinter No.:	
		Applicant's registration No. with the Office	
State (that is, country) of nationality:		State (that is, country) of residence:	
US		US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)			
ALLAN, Bernard 940 Guerrero Street San Francisco, CA 94110 United States of America			
State (that is, country) of nationality:		State (that is, country) of residence:	
IE		US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)			
GREGOIRE, Francine 1044 Carol Lane Lafayette, CA 94549 United States of America			
State (that is, country) of nationality:		State (that is, country) of residence:	
BE		US	
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.			

## Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet should not be included in the demand.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LAVAN, Brian  
2020 Lawton Street  
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United States of America

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GB

State *(that is, country)* of residence:

US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MOODIE, Shonna  
2091 Golden Gate Avenue  
San Francisco, CA 94115  
United States of America

State *(that is, country)* of nationality:

GB

State *(that is, country)* of residence:

US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WATERS, Steve  
1 Lobelia Lane  
San Ramon, CA 94583  
United States of America

State *(that is, country)* of nationality:

US

State *(that is, country)* of residence:

US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WONG, Chi-Wai  
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State *(that is, country)* of nationality:

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State *(that is, country)* of residence:

US

☐ Further applicants are indicated on a continuation sheet.

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation.  
The address must include postal code and name of country.)*HINSCH, Matthew E  
TOWNSEND AND TOWNSEND AND CREW LLP  
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United States of America

Telephone No.:

415-576-0200

Facsimile No.:

415-576-0300

Teleprinter No.:

Agent's registration No. with the Office

47,651

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:\***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☒ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☒ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- |  |   |    |        |
|--|---|----|--------|
| 1. translation of international application                              | : |    | sheets |
| 2. amendments under Article 34   | : | 12 | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : |    | sheets |
| 4. copy (or, where required, translation) of statement under Article 19  | : |    | sheets |
| 5. letter  | : | 1  | sheets |
| 6. other ( <i>specify</i> )  | : |    | sheets |

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received not received

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item (s) marked below:

- |  |   |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 5. <input type="checkbox"/> statement explaining lack of signature                          |
| 2. <input type="checkbox"/> original separate signed power of attorney                   | 6. <input checked="" type="checkbox"/> sequence listing in computer readable form           |
| 3. <input type="checkbox"/> original general power of attorney;                          | 7. <input type="checkbox"/> tables in computer readable form related to sequence listings   |
| 4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 8. <input type="checkbox"/> other ( <i>specify</i> ) Transmittal Letter, Postcard, Diskette |

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

X

Matthew E. Hinsch  
TOWNSEND AND TOWNSEND AND CREW LLP  
USPTO Reg. No.: 47,651  
Applicants' Agent

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- |  |   |
|--|---|
| 1. Date of actual receipt of DEMAND:   |   |
| 2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):   |   |
| 3. <input type="checkbox"/> The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.                        | <input type="checkbox"/> The applicant has been informed accordingly. |
| 4. <input type="checkbox"/> The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.                               |   |
| 5. <input type="checkbox"/> Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. |   |

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Demand received from IPEA on:

## 2. Size Differential Filtration

[0085] Based on a calculated molecular weight, a protein of greater and lesser size can be isolated using ultrafiltration through membranes of different pore sizes (for example, Amicon or Millipore membranes). As a first step, the protein mixture is ultrafiltered through a membrane with a pore size that has a lower molecular weight cut-off than the molecular weight of the protein of interest. The retentate of the ultrafiltration is then ultrafiltered against a membrane with a molecular cut off greater than the molecular weight of the protein of interest. The recombinant protein will pass through the membrane into the filtrate. The filtrate can then be chromatographed as described below.

## 3. Column Chromatography

[0086] The proteins of interest can also be separated from other proteins on the basis of their size, net surface charge, hydrophobicity and affinity for ligands. In addition, antibodies raised against proteins can be conjugated to column matrices and the proteins immunopurified. All of these methods are well known in the art.

[0087] Immunoaffinity chromatography using antibodies raised to a variety of affinity tags such as hemagglutinin (HA), FLAG, Xpress, Myc, hexahistidine (SEQ ID NO:113) (His), glutathione S transferase (GST) and the like can be used to purify polypeptides. The His tag will also act as a chelating agent for certain metals (e.g., Ni) and thus the metals can also be used to purify His-containing polypeptides. After purification, the tag is optionally removed by specific proteolytic cleavage.

[0088] It will be apparent to one of skill that chromatographic techniques can be performed at any scale and using equipment from many different manufacturers (e.g., Pharmacia Biotech).

## **IV. DETECTION OF POLYNUCLEOTIDES OF THE INVENTION**

[0089] Those of skill in the art will recognize that detection of expression of polynucleotides and polypeptides of the invention has many uses. For example, as discussed herein, detection of levels of polynucleotides and polypeptides of the invention in a patient is useful for diagnosing diabetes or a predisposition for at least some of the pathological effects of diabetes. Moreover, detection of gene expression is useful to identify modulators of expression of polynucleotides and polypeptides of the invention.

interleukin receptors, immunoglobulin receptors and antibodies, the cadherin family, the integrin family, the selectin family, and the like; *see, e.g., Pigott & Power, The Adhesion Molecule Facts Book I* (1993)). Similarly, toxins and venoms, viral epitopes, hormones (*e.g., opiates, steroids, etc.*), intracellular receptors (*e.g., which mediate the effects of various small*  
5 *ligands, including steroids, thyroid hormone, retinoids and vitamin D; peptides*), drugs, lectins, sugars, nucleic acids (both linear and cyclic polymer configurations), oligosaccharides, proteins, phospholipids and antibodies can all interact with various cell receptors.

[0165] Synthetic polymers, such as polyurethanes, polyesters, polycarbonates, polyureas,  
10 polyamides, polyethyleneimines, polyarylene sulfides, polysiloxanes, polyimides, and polyacetates can also form an appropriate tag or tag binder. Many other tag/tag binder pairs are also useful in assay systems described herein, as would be apparent to one of skill upon review of this disclosure.

[0166] Common linkers such as peptides, polyethers, and the like can also serve as tags,  
15 and include polypeptide sequences, such as poly-Gly sequences of between about 5 and 200 amino acids (SEQ ID NO:114). Such flexible linkers are known to those of skill in the art. For example, poly(ethylene glycol) linkers are available from Shearwater Polymers, Inc., Huntsville, Alabama. These linkers optionally have amide linkages, sulfhydryl linkages, or heterofunctional linkages.

[0167] Tag binders are fixed to solid substrates using any of a variety of methods currently  
20 available. Solid substrates are commonly derivatized or functionalized by exposing all or a portion of the substrate to a chemical reagent that fixes a chemical group to the surface that is reactive with a portion of the tag binder. For example, groups that are suitable for attachment to a longer chain portion would include amines, hydroxyl, thiol, and carboxyl groups.

25 Aminoalkylsilanes and hydroxyalkylsilanes can be used to functionalize a variety of surfaces, such as glass surfaces. The construction of such solid phase biopolymer arrays is well described in the literature (*see, e.g., Merrifield, J. Am. Chem. Soc.* 85:2149-2154 (1963) (describing solid phase synthesis of, *e.g., peptides*); Geysen *et al., J. Immun. Meth.* 102:259-274 (1987) (describing synthesis of solid phase components on pins); Frank and Doring,  
30 *Tetrahedron* 44:6031-6040 (1988) (describing synthesis of various peptide sequences on cellulose disks); Fodor *et al., Science*, 251:767-777 (1991); Sheldon *et al., Clinical Chemistry*. 39(4):718-719 (1993); and Kozal *et al., Nature Medicine* 2(7):753-759 (1996) (all describing





TGCATAGTGAGTGACTTGGGCCTTCACAAACAGGGTGTGGAGTGGCAGGCAGAGGCCTCTAAATCTCAGGGCAAACATGGTGA  
ATCTATCTCTCCGGAGATAATTTTCATACAGAGATTTTAAGAAAACATCTTTATATTAAAAACAGATCTCATTTGATCCTTAAA  
AAAAAAAAAAAAAAAAAAAA

5 **SEQ ID NO:68 Human (R)-3-hydroxybutyrate dehydrogenase polypeptide sequence**

protein\_id:gi17738292

MLATRLSRPLSRLPGKTLSDRENGARRPLLLGSTSFIPIGRRTYASAAEPVGSKAVLVTGCDSGFGFSLAKHL  
HSKGFLVFAGCLMKDKGHDGVKELDSLNSDRLRTVQLNVCSSEVEKVVVEIVRSSLKDPEKGMWGLVNNAGISTF  
GEVEFTSLETYKQVAEVLWGTVMRTKSFLLPLIRRAKGRVVNISSMLGRMANPARSPYCITKFGVEAFSDCLRYE  
10 MYPLGVKVSVVEPGNFIAATSLYSPESIQIAIAKKMWEELPEVVRKDYGKKYFDEKIAKMETYCSSGSTDTSPVID  
AVTHALTATTPYTRYHPMDYYWLRMQIMTHLPGAISDMIYIR

**SEQ ID NO:69 Mouse(R)-3-hydroxybutyrate dehydrogenase nucleotide sequence**

accession:BC027063

15 GGACAAAGGTGATGCTGGGGTCAAGGAAGTGGACAGCTTGAAGAGTGACCGACTGAGAACCATCCAGCTCAATGT  
CTGCAACAGTGAAGAGGTGGAGAAGGCGGTGGAGACGATCCGCTCCGGCCTGAAAGATCCTGAGAAGGGAATGTG  
GGGCCTGGTTAAACAACGCAGGCATCTCAACGTTTGGGGAGGTGGAGTTCACCAGCATGGAGACATATAAGGAGGT  
GGCTGAAGTGAACCTCTGGGGAACCGTGCGCACCACAAAATCCTTCCCTTCCCCTTCTCCGAAGAGCCAAAGGTCG  
20 CGTCGTAAACATCAGCAGCATGCTGGGCCGCGATGGCCAACCCCGCCCGCTCGCCATACTGCATCACCAAGTTTGG  
GGTCGAGGCTTTCTCGGACTGCCTGCGCTATGAGATGCACCTCTGGGTGTCAAGGTCAGTGTGGTGGAAACCTGG  
CAACTTCATAGCGGCCACCAGTCTCTACAGCCCCGAGCGCATCCAGGCCATCGCCAAGAAGATGTGGGATGACCT  
GCCTGAGGTGCTCCGCAAGGACTATGGCAGGAAGTACTTCGATGAAAAGATTGCCAAGATGGAAACCTACTGCAA  
CAGCGGTTCCACAGATACTTCCTCTGTCATCAACGCTGTACACACGCCTTGACCGCCGCCACCCCGTATACCCG  
25 CTACCATCCCATGGACTACTACTGGTGGCTTCGGATGCAGATCATGACCCATTTTCTGGAGCCATCTCTGACAA  
GATCTACATACTGAAGAGCTGAAGAGGTCCCTTCGGTCTCCGCCAGGGAACCTGGTGGGAGGGAGAAAGATGA  
GGGGAGGGAGTTTACCTTTTGATTAGCTATTGAGGATTACCCACTGTCTTAGGAAGACCTATTTTAACTTACGT  
GTTCAATGTGGTGAATGTTTGGGCCTTCACAAATTAGGGGGGGGGGGCGGAGGGCGCAGGTGGGTGGCCCTAAA  
CCTCAGGGCCAATATGGTGCTTCTATCTATCTCGAGTTGATTTTATATAAAGATTTGTGGGGAAATATCTTTATA  
TTAAAAGCAGGTTATTAGAATAGAATCCAAAATCATTTTCCAGCCAAAACATCCATTGCAAATCTGTATCCCAT  
30 TGATCCTTATGTAAGTCTCATGAGTAAACAGAACAGAATTTTTTTTTTCTGTGTGCATGAAAGAATTTGCAGAT  
CGCAGAGGACATACGAGACACCTCTTTCATTGTGTCCACGGAGTCCCGCCAGTGTTACGGCAAAGGCAAATCACA  
TTTGTGTCCACAGACACTTGAACCCATCAGTCCAGTAACCTGTGACCAACTCTGTACCTTCTCCTGAGCCAGT  
CACACCAAAGGTCACTGTGTGCTATGTCTCTGTGCGTCCGTAGCTCTGTGTGACTGGTGGCCAGCAGTCAGTGAC  
TCTCTGCTGGCTCCAGGTGGGGGAATCCAGAGACTTTTTCAGCTGAGATCTTGGCATTCTCATTAAAGATTTCGAGT  
35 TAGGTCTGGGTGAAGATGCTGTCCGGCTAAGAGCGCAGCTTGGTTTTGCCTAGGACAGGATTGGTGCTATGCTTG  
GTGCTGCAAACAGACCAGTGGTGCCAAGGCTGGGCACTGAGACACTTGCCAGCAATGGGTCTAGATGCCTGTTG  
TCTTGTGTGCTCATGTGGTGCTCCACATGTGGGTGCGTGTGTGCATGCACTCACACACACACACACACACAT

CACACACACACACACACATCACACACACACACACACACCTGCTCCATAGACTTCAGGGTGGTCACCTCTTCTT  
 TGTATTGGGAACCTTCTTTTAAATTAAGTGAAGACACAGTTAGAGAGCCTGTGTTCTCAATCAAGGGACTTTTGCA  
 TTTGAAGGCTGCTTGTCCCTGAAGTTTCTTAGGGTCTCAGTATTTGGATCCAAACCAAATCCCACCACGTTCCAG  
 GTGGCAGCAAGTCTTGGGCCGGGTATTTAAGTGCCAGCTTTACACACATCTCAGCTTTACACTTTTGTGCATCTT  
 5 GTTGCAAAGTCTAGGACTGCCACTAGAGGGCGCGCTGCCCCCTCAACTGGAGCCTGCTCAGGCCCGGGCGTTTTTC  
 GTTCACACAAACTTGGGGTCTTTTCAAGAGTGTGTTGACCACCTACTTGGACACTGCCAGGGAACAAAGAGAAGAG  
 CAAAGACCCCTTGGAAACCGATCCTACACTCCTGGCAGTGTCTAGCCTGAAACTGAAGCCCAGCGCCAGGAGAA  
 AGCAAAGGAACCTGGACAGCCACAGGCGGGTGCAGGCAGTGTCTAGACAAAGAGGGTCCCACAGAGAGCGAATTC  
 AGCCTGCCGGTTTTGGGCTTTTAAACCCCTCTGGATACAAACAGAGGTGCACTGTTCTAGCTCCTGTCTTCAAAGCA  
 10 AAGTAGATAGGGCCTGAGAGGGAAGGTGAGAGGGAGCCAGGGCCCCAGGGTCCACGAATTTACCTGACAGCGGGA  
 TGCATTTGTACTGCAGAGCCTGCCTCCTGCTGGCGTCTTTTCAAGTGGCATTTTACACCTTGGGAGAATTTGTATCC  
 GTGTTTAATAAAGAGATTGGTCATAACAAAAAAAAAAAAAAAAA

**SEQ ID NO:70 Mouse (R)-3-hydroxybutyrate dehydrogenase polypeptide sequence**

15 accession:gi20071589  
 DKGDAGVKELDSLKSDRLRTIQLNVCNSEEVEKAVETIRSLKDPKGMWGLVNNAGISTFGEVEFTSMETYKEV  
 AEVNLWGTVRTTKSFLPLLRRAKGRVNISSMLGRMANPARSPYCITKFGVEAFSDCLRYEMHPLGVKVSVEPG  
 NFIAATSLYSPERIQAIKKMWDDLPEVVRKDYGRKYFDEKIAKMETYCNSGSTDTSSVINAVTHALTAATPYTR  
 YHPMDYYWLRMQIMTHFPGAISDKIYIH

20 **SEQ ID NO:71 Rat (R)-3-hydroxybutyrate dehydrogenase nucleotide sequence**  
 accession:NM\_053995

CCCTCAATAGCCACACTATTTATTTTATTTCAATTAAAAATTTCTTCCCAAACCTTTCCTGCACCTCCCTCACCC  
 AAAACTATAAACTCGGTGCCATGATGCTGGCCGCCCGTCTTTCCAGACCCCTGTACAGCTCCCAGGAAAAGCTC  
 25 TAAGTGTCTGTGATAGAGAAAATGGGACAAGACACACACTGTTGTTTTACCCAGCTTCTTTCAGCCCTGACACCC  
 GTCGGACCTACACCAGCCAGGCAGATGCGGCTAGTGGCAAAGCTGTCTGGTTACAGGCTGTGACTCTGGATTTG  
 GGTTCTCTTTGGCCAAGCATCTACACTCAAAAGGTTTCTTGTATTTGCCGGATGTTTGTGAAGGAACAAGGCG  
 ATGCTGGGGTCAGGGAGCTGGACAGCCTGAAGAGTGACCGGCTGAGAACCATCCAGCTCAATGTCTGCAACAGTG  
 AGGAGGTGGAGAAAGCGGTGGAGACCGTCCGCTCCGGCCTGAAGGATCCTGAGAAGGGAATGTGGGGCCTGGTTA  
 30 ACAACGCAGGCATCTCAACGTTTGGGGAGGTGGAGTTCACTAGCATGGAGACGTATAAGGAGGTGGCCGAAGTGA  
 ACCTCTGGGGAACTGTGCGCACAACAAAATCCTTCTTCCCTTCTCCGAAGAGCCAAAGGCCGTGTTGTTAACA  
 TCAGCAGCATGCTGGGTGCGATGGCCAACCCAGCCCGCTCACCATACTGCATCACCAAGTTTGGGGTAGAGGCTT  
 TCTCGGACTGCCTACGCTATGAGATGCACCTCTGGGTGTGAAGGTCAAGTGTGGTGGAGCCTGGCAACTTCATAG  
 CTGCCACCAGCCTCTATAGCCCTGAGCGTATCCAGGCCATTGCCAAGAAGATGTGGGATGAGCTGCCAGAGGTCTG  
 35 TCCGCAAAGACTATGGCAAGAAGTACTTCGATGAAAAGATTGCCAAGATGGAGACCTACTGCAACAGCGGTTCCA  
 CCGATACGTCCTCCGTATCAACGCTGTACCCATGCCCTGACTGCTGCCACCCCTTATACCCGCTACCATCCCA  
 TGGACTACTACTGGTGGCTGCGGATGCAGGTCATGACCCATTTTCTGGAGCCATCTCTGACAAGATCTACATAC

ACTGAAGAGCTGAAGAGGTCCCTGCAGCCTCTGCCAGGGAGCCTGATGGGAGGGAGTTCATACAGTTATCTTTTG  
ATTAACCATTGTGGGTTGTCCACTGTCTTAGGAAGACCTATTTTAACTTACGTGTTCAATGTGGTGAATGGTTT  
GGGCCTTCACAAATACAGGGCACTGGTGGGTGGCCCTAACCTCAAGGCCAATATGGTGCTTCTATCTGTCTATC  
TAGAGTTGATTTTATATAAAGATTTGTGGGAAATACCTTTATATTAAAGACGTTATTAGAATAGAAAAAA

5

**SEQ ID NO:72 Rat (R)-3-hydroxybutyrate dehydrogenase polypeptide sequence**

accession:gi16758902

MMLAARLSRPLSQLPGKALSVCDRENGTRHTLLFYPAFSPDTRRTYTSQADAASGKAVLVTGCDSGFGFSLAKH  
LHSGKFLVFAGCLLKEQGDAGVRELDLSDRLRTIQLNVCNSEEVEKAVETVRSGLDPEKGMWGLVNNAGIST  
10 FGEVEFTSMETYKEVAEVLWGTVRTTKSFLPLLRRAKGRVNNISSMLGRMANPARSPYCITKFGVEAFSDCLRY  
EMHPLGVKVSVEPGNFIAATSLYSPERIQAIKKMWDELPEVVRKDYGKKYFDEKIAKMETYCNSGSTDTSSVI  
NAVTHALTAATPYTRYHPMDYYWWLRMQVMTHFPGAISDKIYIH

**SEQ ID NO:73 Human aldehyde reductase nucleotide sequence**

15 HUM223359                      accession: J04794    +            CDS:61..1038

AGCCAGAAATGTGAAGTGCTAGCTGAAGGATGAGCAGCAGCTAGCCAGGCAAAGGGGGCAATGGCGGCTTCCTGT  
GTTCTACTGCACACTGGGCAGAAGATGCCTCTGATTGGTCTGGGTACCTGGAAGAGTGAGCCTGGTCAGGTAAAA  
GCAGCTGTTAAGTATGCCCTTAGCGTAGGCTACCGCCACATTGATTGTGCTGCTATCTACGGCAATGAGCCTGAG  
ATTGGGGAGGCCCTGAAGGAGGACGTGGGACCAGGCAAGGCGGTGCCTCGGGAGGAGCTGTTTGTGACATCCAAG  
20 CTGTGGAACACCAAGCACCCACCCGAGGATGTGGAGCCTGCCCTCCGGAAGACTCTGGCTGACCTCCAGCTGGAG  
TATCTGGACCTGTACCTGATGCACTGGCCTTATGCCTTTGAGCGGGAGACAACCCCTTCCCAAGAATGCTGAT  
GGGACTATATGCTACGACTCCACCCACTACAAGGAGACTTGAAGGCTCTGGAGGCACTGGTGGCTAAGGGGCTG  
GTGCAGGCGCTGGGCCTGTCCAACCTCAACAGTCGGCAGATTGATGACATACTCAGTGTGGCCTCCGTGCGTCCA  
GCTGTCTTGCAGGTGGAATGCCACCCATACTTGGCTCAAATGAGCTAATTGCCCCACTGCCAAGCACGTGGCTTG  
25 GAGGTAAGTCTTATAGCCCTTTGGGCTCCTCTGATCGTGCATGGCGTGATCCTGATGAGCCTGTCCTGCTGGAG  
GAACCAGTAGTCCTGGCATTGGCTGAAAAGTATGGCCGATCTCCAGCTCAGATCTTGCTCAGGTGGCAGGTCCAG  
CGGAAAGTGATCTGCATCCCCAAAAGTATCACTCCTTCTCGAATCCTTCAGAACATCAAGGTGTTTGACTTCACC  
TTTAGCCCAGAAGAGATGAAGCAGCTAAATGCCCTGAACAAAAATTGGAGATATATTGTGCCTATGCTTACGGTG  
GATGGGAAGAGAGTCCCAAGGGATGCAGGGCATCCTCTGTACCCCTTAATGACCCGTACTGAGACCACAGCTTC  
30 TTGGCCTCCCTTCAGCTCTGCAGCTAATGAGGTCTGCCACAACGGAAAGAGGGAGTTAATAAAGCCATTGGAG  
CATCCAT

**SEQ ID NO:74 Human aldehyde reductase polypeptide sequence**

protein\_id:gi178481

35 MAASCVLLHTGQKMLPLIGLGTWKSEPGQVKAADVYALSVGYRHIDCAAITYGNEPEIGEALKEDVPGKAVPREEL  
FVTSKLWNTKHHPEDVEPALRKTLADLQLEYLDLYLMHWPYAFERGDNPFPKNADGTICYDSTHYKETWKALEAL  
VAKGLVQALGLSNFNSRQIDILSVASVRPAVLQVECHPYLAQNELIAHCQARGLEVTAYSPLGSSDRAWRPDE

**SEQ ID NO:103 Human TRP-MET nucleic acid sequence**

gi|187558|gb|J02958.1|

CDS:195..4421

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**SEQ ID NO:104 Human TRP-MET polypeptide sequence**

gi|307196|gb|AAA59591.1|

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**SEQ ID NO:105 Mouse TRP-MET nucleic acid sequence**

gi|6678867|ref|NM\_008591.1|

CDS:1..4140

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# **SEQ ID NO:106 Mouse TRP-MET polypeptide sequence**

gi|6678868|ref|NP\_032617.1|

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SQCLSAPYFIQCGWCHNQCVRFDECPSGTWTQEICLPAVYKVFP TSAPLEGGTVLTICGWDFGFRKNNKFDLRKT  
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LTGKYLNSGNSRHISIGGKTCTLKSVSDSILECYTPAQTTSEFPVKLKIDLANRETSSFSYREDPVVYEIHPTK  
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TRGAPPYPDVNTFDITIYLLQGRLLQPEYCPDALYEVMLKCWHPKAEMRPSFSELVSRISSIFSTFIGEHYVHV  
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**SEQ ID NO:107 Rat TRP-MET nucleic acid sequence**

gi|13928699|ref|NM\_031517.1|

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AGAAGACTCTTGCAACCAGAGTACTGTCCAGACGCCTTGTATGAAGTGATGCTAAAATGCTGGCACCCCAAAGCA  
GAAATGCGCCCATCGTTTTCTGAACTGGTCTCCAGAATATCCTCAATCTTCTCCACTTTCATTGGCGAGCACTAT  
GTCCATGTGAACGCTACTTATGTGAATGTAAAATGTGTTGCTCCATATCCTTCTCTGTGTCATCCCAAGACAAC  
ATTGACGGCGAAGCGAACACATGACGGATAAGAGGCCGCCAGCCCACTTCCAAGAAACAGTTC

# SEQ ID NO:108 Rat TRP-MET polypeptide sequence

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MKAPTALAPGILLLLTLAQRSHGECKEALVKSEMNVMNKYQLPNFTAETPIQNVVLHGHHIYLGATNYIYVLND  
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AADIQSEVHCFMSPLAEESGQCPDCVVSALGAKVLLSEKDRFINFFVGNTINSSYPDYSLHSISVRLKETQD  
GFKFLTDQSYIDVLGEFRDSYPIKYIHAFESNHFYFLTVQKETLDAQTFHTRIIRFCSVDSGLHSYMEMPLECI  
LTEKRRKRSTREEVFNILQAAVYSKPGANLAKQIGASPYDDILYGVFAQSKPDSAEPMNRSAVCAFPKIYVNDFF  
NKIVNKNVRCLOHFGYGNHEHCFNRTLNRSSGCEVRSDEYRTEFTTALQAVDLFMGRNLNVLLTSISTFIKGD  
LTIANLGTSEGRFMQVVLRSRTAHFTPHVNFLLDSHPVSPEVIVEHPSNQNGYTLVVVGKKITKIPLNGLGCGHFQ  
SCSQCLSAPYFIQCGWCHNRCVHSNECPSGTWTQEICLPVYKVFPSTAPLEGGTMLTICGWDGFGKKNKFDLR  
KTKVLLGNESCTLTLESTNTLKCTVGPAMSEHFNVSIVSNSRETTQYSAFSYVDPVITSISPRYGPHAGGTL  
LTLTGKYLNSGNSRHISIGGKCTLKSVSDSILECYTPGHTVSAEFPVKLKIDLADRVTSFSYGEDPPFVSEIHP  
TKSFISGGSTITGIGKNLSVSTPKLVIEVHDVGVNVTACQHRSSSEIICCTTPSLQQLDLQLPLKTKAFFLLD